Journal of the American College of Cardiology
Vol. 58, No. 7, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.01.065

Published by Elsevier Inc.

Cardiac Imaging

Impaired Myocardial Flow Reserve on Rubidium-82 Positron Emission Tomography Imaging Predicts Adverse Outcomes in Patients Assessed for Myocardial Ischemia

Maria C. Ziadi, MD,* Robert A. deKemp, PhD,* Kathryn A. Williams, MS,† Ann Guo, MEng,* Benjamin J. W. Chow, MD,* Jennifer M. Renaud, MSc,* Terrence D. Ruddy, MD,* Niroshi Sarveswaran, BHSc,* Rebecca E. Tee, MSc,* Rob S. B. Beanlands, MD*

Ottawa, Ontario, Canada

Objectives We evaluated the prognostic value of myocardial flow reserve (MFR) using rubidium-82 (^{82}Rb) positron emission tomography (PET) in patients assessed for ischemia.

Background The clinical value of MFR quantification using ^{82}Rb PET beyond relative myocardial perfusion imaging remains uncertain.

Methods We prospectively enrolled 704 consecutive patients; 677 (96%) completed follow-up (median 387 days [interquartile range: 375 to 416 days]). Patients were divided into 4 groups: I, normal summed stress score (SSS) (<4) and normal myocardial flow reserve (MFR) (>2); II, normal SSS and MFR <2; III, SSS ≥ 4 and MFR ≥ 2; IV, SSS ≥ 4 and MFR <2.

Results For patients with a normal SSS and those with an abnormal SSS, there were significant differences in outcomes for hard events (cardiac death and myocardial infarction) between patients with MFR ≥ 2 and those with MFR <2 (I: 1.3% vs. II: 2% [$p = 0.029$]; III: 1.1% vs. IV: 11.4% [$p = 0.05$]) and for major adverse cardiac events (MACE) ($p = 0.003$ and $p < 0.001$, respectively). In the adjusted Cox model, MFR was an independent predictor of hard events (hazard ratio: 3.3; 95% confidence interval: 1.1 to 9.5; $p = 0.029$) and MACE (hazard ratio: 2.4, 95% confidence interval: 1.4 to 4.4, $p = 0.003$). The incremental prognostic value of the MFR over the SSS was demonstrated by comparing the adjusted SSS model with and without the MFR for hard events ($p = 0.0197$) and MACE ($p = 0.002$).

Conclusions MFR quantified using ^{82}Rb PET predicts hard cardiac events and MACE independent of the SSS and other parameters. Routine assessment of ^{82}Rb PET–quantified MFR could improve risk stratification for patients being investigated for ischemia. (J Am Coll Cardiol 2011;58:740–8) © 2011 by the American College of Cardiology Foundation

The diagnostic and prognostic value of relative myocardial perfusion imaging (MPI) using single-photon emission tomography (1,2) and positron emission tomography (PET) (3–6) is well established. Relative MPI has limitations because it often uncovers only the territory supplied by the most severe coronary stenosis. This could underestimate the extent of coronary artery disease (CAD) (6–8). Also, relative MPI cannot define the presence of subclinical atherosclerosis.

See page 749

In addition to relative MPI, PET imaging enables noninvasive quantification of myocardial perfusion. Various clinical applications for myocardial flow reserve (MFR) (stress myocardial blood flow [MBF]/rest MBF) have been proposed (8–15). To date, however, MFR measurement has not been integrated into clinical practice because studies demonstrating added clinical value have been limited.

From the *National Cardiac PET Centre, Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; and the †Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. The project was supported in part by the Molecular Function and Imaging Program (HSFO PRG6242). Dr. Ziadi was a Research Fellow supported by University of Ottawa International Fellowship Award and the Molecular Function and Imaging Program (HSFO PRG6242). Dr. deKemp is a consultant to DraxImage; and has received grant funding from a government/industry program (GE Healthcare and MDS Nordion). Dr. Ruddy received grant support and honoraria from GE Healthcare and MDS Nordion. Dr. Beanlands is a consultant to Jubilant DraxImage and Lantheus Medical Imaging; has received research grants from Lantheus Medical Imaging, GE Healthcare, and MDS Nordion; and is a Career Investigator supported by the Heart and Stroke Foundation of Ontario (HSFO). All other authors have reported that they have no relationships to disclose.

Manuscript received August 2, 2010; revised manuscript received January 25, 2011, accepted January 31, 2011.

Among available validated PET tracers for flow quantification, rubidium-82 (^{82}Rb) has the most potential for broad clinical application. It is more widely available in North America than other cyclotron-based PET tracers. Still, there are no large studies that evaluated the prognostic value of flow quantification using ^{82}Rb PET. If the added prognostic value of MFR quantification with ^{82}Rb were demonstrated, this could have an important impact given the growing use of ^{82}Rb PET worldwide.

We sought to assess the prognostic value of ^{82}Rb PET–quantitated MFR in patients being investigated for ischemia. We hypothesized that patients with reduced MFR would have higher cardiac event rates than those with preserved MFR and ^{82}Rb MFR would be an independent predictor of adverse outcomes.

Methods

Patient population. We prospectively enrolled patients with known or suspected CAD, referred for dipyridamole ^{82}Rb PET MPI for evaluation of ischemia at the University of Ottawa Heart Institute, Ottawa, Ontario, Canada. All patients provided written informed consent for inclusion in the study.

Patients were excluded if they did not have MBF data available because dynamic acquisition was not acquired or because of other technical factors (16). Patients who underwent dobutamine, exercise, and/or ^{13}N-ammonia ($^{13}NH_3$) PET were also excluded. For those with more than 1 ^{82}Rb PET scan, only the first scan was used.

PET imaging. Patients refrained from caffeine ≥12 h and theophyllines for >48 h before the MPI study (17,18). Antianginal medications were withheld the morning of the test. After an overnight fast, patients were positioned in a 3-dimensional PET system (Discovery Rx/VCT, GE Healthcare, Milwaukee, Wisconsin) (19). A low-dose (~0.5 mSv), fast helical (1.5 s) computed tomography scan (120 kpv with axial and angular milliampere modulation at a noise index of 50) was acquired for attenuation correction. Then, 10 MBq/kg of ^{82}Rb was administered intravenously using a custom elution system to ensure dead-time losses remained <50% (20,21). A 17-frame, 10-min dynamic ^{82}Rb scan was acquired with a parallel list-mode acquisition.

Pharmacological stress and imaging. After rest PET MPI, a dipyridamole stress test was performed (0.14 mg/kg/min over 5 min). Then 10 MBq/kg of ^{82}Rb was infused 3 min after completion of the vasodilator infusion. Stress images were acquired per rest MPI. A repeat low-dose computed tomography scan was acquired after stress images for attenuation correction.

Image processing. Images were reconstructed using Fourier rebinning and filtered back-projection with a 12-mm 3-dimensional Hann window of the ramp filter. Automatic reorientation of the images, automatic extraction of mean myocardial and cavity time-activity curves (21,22), and generation of polar maps of absolute MBF and MFR were performed using our FlowQuant software (Ottawa Heart Institute Research Corporation, Ottawa, Ontario, Canada) (16).

Electrocardiographic gating. The list-mode data from 2.5 to 10 min were replayed to reconstruct electrocardiographic-gated images. Left ventricular ejection fractions (LVEFs) were determined using 4DM software (INVIA, Ann Arbor, Michigan).

^{82}Rb PET analysis. STATIC IMAGE INTERPRETATION. Images were interpreted using a 17-segment model (23) and a 5-point scoring system blinded to clinical, imaging, and flow data by an experienced blinded observer and then independently compared with the clinical imaging report. Any discrepancies were then reviewed independently by an additional experienced blinded observer. Any remaining discrepancies were settled by consensus. Summed stress score (SSS), summed rest score, and summed difference score (summed difference score = SSS − summed rest score) were calculated. An SSS ≥4 was considered abnormal (2,14). The LVEF during rest and stress and LVEF reserve (stress-rest LVEF) (6) were determined. The presence or absence of transient ischemic dilation was noted.

^{82}RB FLOW QUANTIFICATION. MBF was quantified using a 1-tissue compartment model with a flow-dependent extraction correction (0). The washout rate was expressed as $k_2 = K_1/DV$; DV, the distribution volume of ^{82}Rb in tissue, was set to a constant value (25) for each scan by fitting the model to the region of normal relative uptake (75% to 100% of maximum). MFR <2.0 was considered abnormal (9,14).

ELECTROCARDIOGRAPHIC ANALYSIS. Stress electrocardiograms were reviewed and interpreted by blinded observers using recommended practice guidelines (26).

Cardiac event definitions and follow-up. The primary outcome was the prevalence of hard cardiac events: myocardial infarction (MI) and cardiac death. A secondary outcome was the prevalence of major adverse cardiac events (MACE): cardiac death, MI, late revascularization (percutaneous coronary intervention or coronary artery bypass graft) and cardiac hospitalization (e.g., acute coronary syndrome and heart failure). Coronary artery bypass graft or percutaneous coronary intervention within 90 days after the PET scan was considered to be triggered by the relative MPI results and therefore censored from analysis (4). Definitions of each variable were described previously (4,27).

Elective admissions for procedures (e.g., implantable cardioverter-defibrillator) were not counted as events. For

Abbreviations and Acronyms

- **CI** = confidence interval
- **HR** = hazard ratio
- **LVEF** = left ventricular ejection fraction
- **MACE** = major adverse cardiac event(s)
- **MFR** = myocardial flow reserve
- **MI** = myocardial infarction
- **MPI** = myocardial perfusion imaging
- **$^{13}NH_3$** = ^{13}N ammonia
- **PET** = positron emission tomography
- **^{82}Rb** = rubidium-82
- **SSS** = summed stress score

patients with ≥2 events, the first event date was considered for analysis.

Follow-up information was acquired for 677 of 704 patients (96%), the majority via telephone interview (successful in 609 of 677 patients; 90%). Events are based on the best available data as of March 2010. When telephone contact was unsuccessful, a record search (n = 12; 2%) was used. Telephone contact with a close family member of the patient was obtained for some patients (n = 56; 8%). Additional data were gathered from medical charts and/or referring physicians. Verification of events was obtained from patient charts, hospital records, death certificates, and/or contact with referring physicians.

Statistical analysis. Multivariable Cox proportional hazards models were used to assess the independent prognostic value of the MFR. Individual predictor's Wald chi-square statistics are provided as an indicator of the relative importance of the predictor. For the MFR and SSS, accepted cutoff values were used to create the variables of primary interest. Adjusted Kaplan-Meier curves illustrate the incremental value of the MFR over the SSS. Cox model contrasts were used to test for all MFR and SSS group differences. Interactions between the MFR and SSS were tested in the models and were not statistically significant. Therefore, the SSS and MFR could be assessed as independent predictors without the interaction.

To prevent overfitting of the multivariable Cox proportional hazards models, only baseline characteristics included in Tables 2 and 3 with p values <0.05 with MFR and SSS were considered in the full models. For the hard events model, only 3 significant baseline characteristics (previous MI, stress LVEF, and peripheral vascular disease) were considered in the model with the MFR and SSS. Stepwise selection was used to create the adjusted model controlling for confounding. PVD was not significant in the final hard events model.

To show the incremental value of the MFR, the adjusted model with the SSS + MFR was compared with the model with the SSS alone using a likelihood ratio chi-square test. We demonstrated the added value of the MFR as both a continuous variable and a binary variable. We used the dichotomous variable because it represents a more straightforward way to display in survival curves and odds ratios. The net reclassification improvement and the integrated discrimination improvement were calculated as additional tools.

Patient subgroups. Four groups were generated: I, normal SSS <4 and normal MFR ≥2; II, normal SSS <4 and abnormal MFR <2; III, abnormal SSS ≥4 and normal MFR ≥2; and IV, abnormal SSS ≥4 and normal MFR <2. Hard cardiac events and MACE across different subgroups were evaluated.

Results

Baseline patient characteristics. Among 957 scans performed, 243 were excluded: 48 with dobutamine or exercise stress; 144 $^{13}NH_3$ scans; 20 repeat scans; 40 inadequate or incomplete dynamic data to enable quantification; and 1 patient with previously known dilated cardiomyopathy. Thus, 704 consecutive patients were enrolled: 677 (96%) had successful follow-up, with 58 patients censored due to early revascularization. Median follow-up was 387 days (interquartile range: 375 to 416 days).

The demographic and ^{82}Rb PET imaging characteristics of patients with follow-up are given in Table 1. The characteristics of the patients who were lost to follow-up (n = 27) were similar.

Outcome data. During follow-up, among the 677 patients in this study, there were 27 hard events (4%), 12 cardiac deaths (1.8%), and 16 nonfatal MIs (2.4%) (1 patient had MI and then cardiac death). For MACE, there were 71 first events (71 of 677; 10.5%). Among patients with events, 20 patients (20 of 71; 28%) underwent late revascularization as first events (13 percutaneous coronary interventions, 7 coronary artery bypass grafts), and 29 patients were admitted:

Table 1 Demographics and PET Parameters for Patients With Follow-Up

Variable	No Follow-Up (n = 27)	Follow-Up (n = 677)	p Value
Age, yrs	57 ± 15	64 ± 12	0.006
Male	14 (52)	416 (61)	0.322
Hypertension	18 (67)	461 (68)	0.837
Diabetes	8 (30)	195 (29)	1.000
Smoking	19 (70)	431 (64)	0.545
Family history of CAD	14 (52)	336 (50)	0.847
Hyperlipidemia	20 (74)	467 (69)	0.674
PVD	4 (15)	126 (19)	0.802
Known CAD	14 (52)	390 (58)	0.558
Previous MI	9 (33)	268 (40)	0.554
Previous revascularization	12 (44)	304 (45)	1.000
CCS angina class ≥II	10 (37)	274 (40)	0.842
NYHA functional class ≥II	8 (30)	208 (31)	1.000
^{82}Rb PET standard imaging parameters			
SSS	4.9 ± 5.3	4.3 ± 5.9	0.257
SDS	3.7 ± 4.7	2.4 ± 4.3	0.089
Positive ECG	6 (22)	79 (12)	0.124
TID	2 (7)	52 (8)	1.000
Stress LVEF <50%	5 (19)	171 (25)	0.505
Stress LVEF	60 ± 11	59 ± 16	0.928
Rest LVEF	56 ± 10	53 ± 14	0.630
LVEF reserve	4.6 ± 7.2	5.6 ± 8.6	0.589
^{82}Rb PET absolute flow quantification parameters			
Rest MBF	1.04 ± 0.42	1.03 ± 0.38	0.873
Stress MBF	2.28 ± 0.84	2.24 ± 0.93	0.746
MFR	2.46 ± 1.03	2.31 ± 0.91	0.363
MFD	1.24 ± 0.84	1.21 ± 0.79	0.632

Values are mean ± SD or n (%).

CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; LVEF reserve = stress − rest LVEF; MBF = myocardial blood flow; MFD = myocardial flow difference; MFR = myocardial flow reserve; MI = myocardial infarction; NYHA = New York Heart Association; PET = positron emission tomography; PVD = peripheral vascular disease; ^{82}Rb = rubidium-82; SDS = summed difference score; SSS = summed stress score; TID = transient ischemic dilation.

Table 2 Comparison of Patients With and Without Hard Cardiac Events

Variable	No MI/Cardiac Death (n = 650)	MI/Cardiac Death (n = 27)	p Value
Age, yrs	64 ± 12	64 ± 12	0.924
Male	396 (61)	20 (74)	0.226
Hypertension	441 (68)	20 (74)	0.674
Diabetes	181 (28)	14 (52)	0.015
Smoking	408 (63)	23 (85)	0.023
Family history of CAD	321(49)	15 (56)	0.561
Hyperlipidemia	447 (69)	20 (74)	0.674
PVD	115 (18)	11 (41)	0.009
Known CAD	366 (56)	24 (89)	<0.001
Previous MI	245 (38)	23 (85)	<0.001
Previous revascularization	284 (44)	19 (70)	0.009
CCS angina class ≥II	258 (40)	16 (59)	0.047
NYHA functional class ≥II	197 (30)	11 (41)	0.287
^{82}Rb PET standard imaging parameters			
SSS	4.1 ± 5.7	10.1 ± 7.8	<0.001
SDS	2.3 ± 4.1	5.6 ± 5.7	<0.001
Positive ECG	75 (12)	4 (15)	0.543
TID	48 (7)	4 (15)	0.145
Stress LVEF <50%	155 (24)	16 (59)	<0.001
Stress LVEF	60 ± 15	43 ± 17	<0.001
Rest LVEF	54 ± 14	42 ± 16	<0.001
LVEF reserve	5.8 ± 8.5	0.62 ± 93	0.011
^{82}Rb PET absolute flow quantification parameters			
Rest MBF	1.04 ± 0.38	0.89 ± 0.38	0.018
Stress MBF	2.28 ± 0.91	1.30 ± 0.85	<0.001
MFR	2.33 ± 0.90	1.46 ± 0.70	<0.001
MFD	1.25 ± 0.78	0.41 ± 0.66	<0.001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

13 (13 of 71; 18%) because of congestive heart failure; 15 patients (15 of 71; 21%) due to acute coronary syndrome, and 1 patient (1 of 71; 1.4%) due to other cardiac causes (syncope and chest pain and subsequently acute coronary syndrome).

The results of univariate analysis of baseline demographics, standard PET imaging features, and ^{82}Rb MBF quantification parameters for hard cardiac events are summarized in Table 2 and those for MACE are summarized in Table 3.

Patients were divided into 4 subgroups according to the SSS and MFR (Fig. 1). The distribution of patients across the 4 subgroups and the frequency of hard cardiac events and MACE in each of these are provided in Table 4.

For those with a normal SSS and impaired MFR compared with those with a preserved MFR, there was higher incidence of hard events (2% vs. 1.3%, p = 0.029) and a higher incidence of MACE (9% vs. 3.8%, p = 0.003). Among patients with an abnormal SSS, those with MFR <2 compared with those with a preserved MFR had a higher incidence of hard events (11.4% vs. 1.1%, p = 0.05) and a higher incidence of MACE (24% vs. 9%, p < 0.001).

All cardiac deaths occurred in patients with an abnormal MFR (1 [1%] in group II; 11 [6.5%] in group IV). All patients who experienced cardiac death had a severely impaired MFR (MFR <1.5).

Figure 2 shows adjusted event-free survival curves for hard events and MACE in the different subgroups.

Multivariable Cox models. The ^{82}Rb MFR was an independent predictor of cardiac hard events (hazard ratio [HR]: 3.3, 95% confidence interval [CI]: 1.1 to 9.5); p = 0.029). The incremental prognostic value of the MFR over the SSS was also shown by comparing the adjusted SSS models without and with the MFR (p = 0.0197). When only the SSS (HR: 3.1, 95% CI: 1.2 to 8.1; p = 0.018) and previous MI (HR: 6.0, 95% CI: 2.0 to 18.1; p = 0.002) were considered in the model, both were independent predictors. When stress LVEF was added (HR: 0.82, 95% CI: 0.72 to 0.93; p = 0.002), it was significant. At this point, only MI and stress LVEF were significant in the adjusted model. The SSS and stress LVEF were collinear (ρ = 0.6), which resulted in the SSS not being significant. Adding the MFR to the model resulted in the best fit (likelihood ratio test, p = 0.0197) and confirmed the added independent prognostic value of this parameter (Table 5). With 3 individuals

Table 3 Comparison of Patients With and Without MACE

Variable	No MACE (n = 606)	MACE (n = 71)	p Value
Age, yrs	64 ± 12	63 ± 11	0.740
Male	372 (61)	44 (62)	1.000
Hypertension	413 (68)	48 (68)	1.000
Diabetes	164 (27)	31 (44)	0.005
Smoking	379 (63)	52 (73)	0.090
Family history of CAD	303 (50)	33 (46)	0.617
Hyperlipidemia	418 (69)	49 (69)	1.000
PVD	104 (17%)	22 (31%)	0.009
Known CAD	338 (56)	52 (73)	0.005
Previous MI	222 (37)	46 (65)	<0.001
Previous revascularization	265 (44)	38 (54)	0.131
CCS angina class ≥II	235 (39)	39 (55)	0.010
NYHA functional class ≥II	180 (30)	28 (39)	0.103
^{82}Rb PET standard imaging parameters			
SSS	3.84 ± 5.63	8.17 ± 6.98	<0.001
SDS	2.16 ± 4.03	4.93 ± 5.05	<0.001
Positive ECG	68 (11)	11 (15)	0.326
TID	41 (7)	11 (15)	0.016
Stress LVEF <50%	137 (23)	34 (48)	<0.001
Stress LVEF	60 ± 15	48 ± 18	<0.001
Rest LVEF	54 ± 14	46 ± 17	<0.001
LVEF reserve	6.0 ± 8.5	2.1 ± 9.1	<0.001
^{82}Rb PET absolute flow quantification parameters			
Rest MBF	1.04 ± 0.38	0.92 ± 0.38	0.003
Stress MBF	2.31 ± 0.90	1.61 ± 0.94	<0.001
MFR	2.36 ± 0.91	1.74 ± 0.75	<0.001
MFD	1.27 ± 0.77	0.68 ± 0.74	<0.001

Values are mean ± SD or n (%).
MACE = major adverse cardiac event(s); other abbreviations as in Table 1

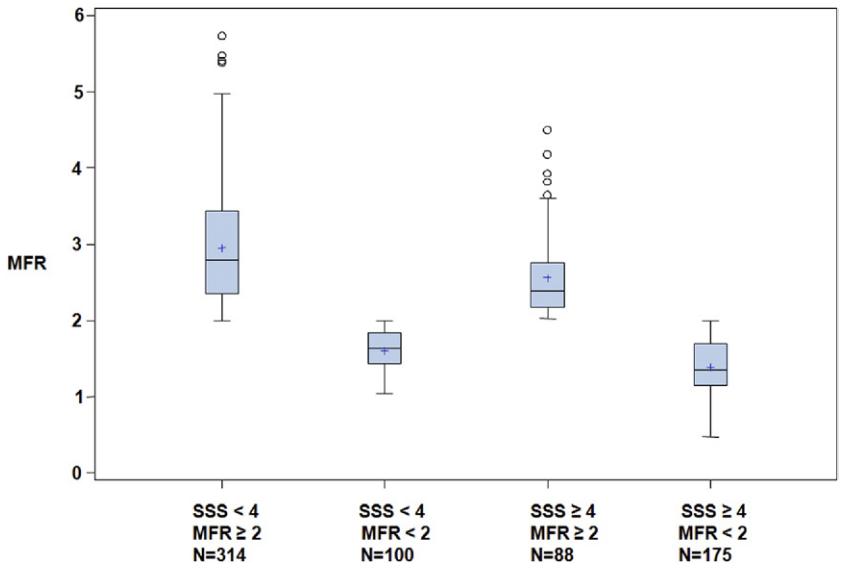

Figure 1 **Box Plots Demonstrating the Distribution of MFR Across Subgroups**

+ = mean; ⊥ = minimum value >1.5 (interquartile range) below the 25th percentile; T = maximum value <1.5 (interquartile range) above the 75th percentile; interquartile range 75th to 25th percentiles; crossbars = 25th, 75th, and 50th (median) percentiles; circles = outliers. HR = hazard ratio; MFR = myocardial flow reserve; SSS = summed stress score.

classified up and 0 classified down with the MFR in the model, the net reclassification improvement was estimated at 0.11 and showed a trend toward significance ($p = 0.092$). The integrated discrimination improvement estimated at 0.009 was significant ($p < 0.001$).

The ^{82}Rb MFR was also an independent predictor of MACE (HR: 2.4, 95% CI: 1.4 to 4.4; $p = 0.003$). In the model without the MFR, the SSS ≥4, diabetes, Canadian Cardiovascular Society (CCS) angina class ≥II and stress LVEF were independent predictors of MACE. The effect of adding the MFR resulted in better fitting of the model ($p = 0.002$), after controlling for the significant covariate SSS (HR: 1.9, 95% CI: 1.03 to 3.6; $p = 0.041$), diabetes, CCS angina class, and stress LVEF (Table 6). This incremental value is also supported by the significant net reclassification improvement (0.112, $p = 0.048$) and integrated discrimination improvement (0.014, $p < 0.001$). Among the flow parameters, the MFR provided the most significant independent prognostic value for both hard events and MACE.

MACE in subgroup categories of SSS and MFR. The percentage of MACE was analyzed at different levels of the SSS: SSS <4, SSS 4 to 7, SSS ≥8. With the aim of understanding the impact of progressive reductions in MFR on outcomes; MACE were evaluated at different degrees of MFR impairment (MFR ≥2, MFR 1.9 to 1.5, MFR <1.5) in different the SSS categories. At any level of the SSS, the incidence of MACE was highest in patients with the lowest MFR (<1.5) (Fig. 3).

Regional MFR. We conducted exploratory analyses in patients with a normal global MFR (≥2). We observed that patients with abnormal regional MFR in a single-vessel territory compared with those with normal MFR in all vascular territories had increased MACE (9 of 94; 9.6% vs. 11 of 300; 3.7%; unadjusted $p = 0.015$, adjusted $p = 0.024$) and a trend for hard events (3 of 94; 3.2% vs. 2 of 300; 0.7%; unadjusted $p = 0.083$, adjusted $p = 0.135$). Among those with normal global MFR and abnormal regional MFR, there was no significant difference in events for those with and without an abnormal SSS. Eight patients with abnormal MFR in

Table 4 **Incidence of Hard Cardiac Events and MACE Across Group Categories**

	SSS <4 (n = 414)			SSS ≥4 (n = 263)		
Outcomes (n = 678)	Group I: MFR ≥2 (n = 314)	Group II: MFR <2 (n = 100)	p Value*	Group III: MFR ≥2 (n = 88)	Group IV: MFR <2 (n = 175)	p Value*
MI/cardiac death (n = 27)	4 (1.3)	2 (2)	0.029	1 (1.1)	20 (11.4)	0.05
MACE (n = 71)	12 (3.8)	9 (9)	0.003	8 (9)	42 (24)	<0.001

Values are n (%). *p values are based on Cox model contrasts.
Abbreviations as in Tables 1 and 3.

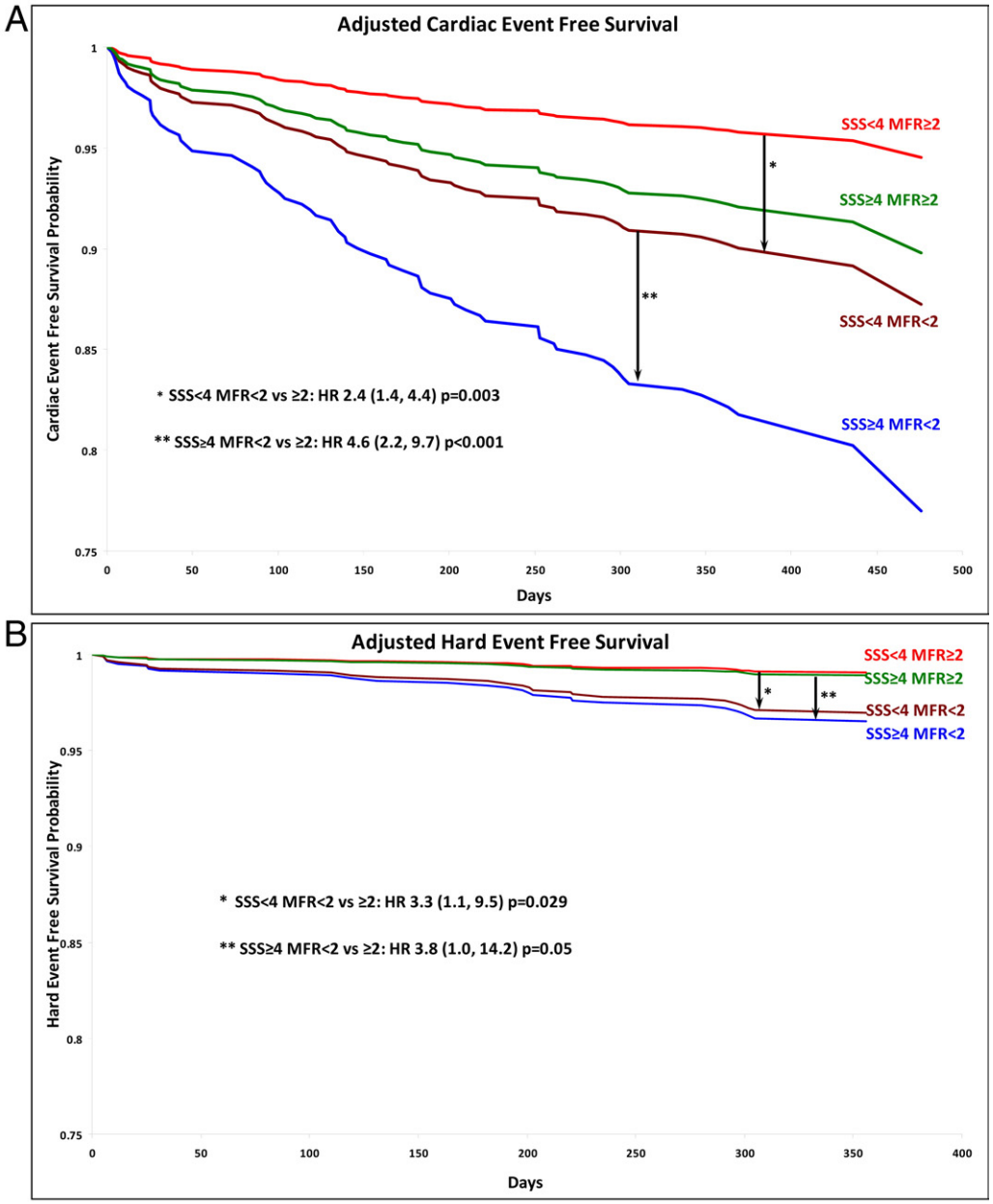

Figure 2 **Adjusted Cardiac Hard Event-Free Survival and Event-Free Survival Curves**

(A) Adjusted cardiac hard event–free survival. **Arrows** highlight the statistically significant differences in outcomes among subgroups. **(B)** Adjusted major adverse cardiac event–free survival. **Arrows** highlight the statistically significant differences in outcomes among subgroups. Abbreviations as in Figure 1.

2 territories were not considered in the comparison. Among those with an impaired global MFR, it was uncommonly (17 of 275; 6.2%) attributable to a significant reduction in MFR in 1 vascular territory. The number of events was too small to allow conclusive comparisons.

Discussion

This study is one of the first to demonstrate the added and independent prognostic value of MFR using ^{82}Rb PET beyond the relative MPI in a large cohort of patients referred for assessment of ischemia. Patients with impaired ^{82}Rb MFR had a higher incidence of hard cardiac events and MACE at approximately 1-year follow-up. In the multivariable model analysis, ^{82}Rb MFR was an independent predictor of hard events and MACE over the SSS.

Comparison with previous PET studies. At least 4 previous studies assessed the prognostic value of standard relative MPI using PET with ^{82}Rb (3–6). These studies are

Table 5 Multivariable Cox Models of Hard Cardiac Events for Prognostic Value of MFR Compared With SSS

Parameter	Chi-Square test	p Value	Hazard Ratio	95% CI	Deviance Statistic
SSS* + MI history					318.747
SSS	5.6	0.018	3.1	1.2–8.1	
MI	10.0	0.002	6.0	2.0–18.1	
SSS* + MI history + stress LVEF†					309.222‡
SSS	0.76	0.382	1.6	0.56–4.5	
MI	8.1	0.005	5.0	1.7–15.4	
Stress LVEF	9.8	0.002	0.82	0.72–0.93	
SSS* + MI history + stress LVEF† + MFR§					303.662‖
SSS	0.07	0.796	1.2	0.39–3.4	
MI	8.4	0.004	5.2	1.7–15.8	
Stress LVEF	5.8	0.016	0.85	0.75–0.97	
MFR	4.8	0.029	3.3	1.1–9.5	

*≥4 vs. <4. †Per 5-U increase. ‡p = 0.002 (likelihood ratio test). §<2 vs. ≥2. ‖p = 0.0197 (likelihood ratio test).
CI = confidence interval; other abbreviations as in Table 1.

difficult to compare because there are important variations in: 1) population; 2) PET technology and protocol; and 3) endpoints. Studies included 367 to 1,442 patients, with 31% to 70% of patients with known CAD and evaluated hard events, MACE, or all-cause mortality (3–6). The studies each concluded that abnormal relative perfusion is associated with a worse prognosis. Two more recent studies showed that there was added prognostic value using the LVEF (5,6). However, none of these studies measured the absolute myocardial flow. Our study is unique because it is the first to assess the prognostic value of MFR for hard events with ^{82}Rb PET in a large population.

In the setting of ischemic heart disease, Tio et al. (15) showed that MFR measured with $^{13}NH_3$ PET predicts adverse outcomes in patients with severe CAD and left ventricular dysfunction who were not candidates for revascularization. This is a different population from that in the current study, which evaluated patients referred for assessment of ischemia including patients with and without known CAD. The current study population was more comparable to that of Herzog et al. (14) who demonstrated the incremental utility of the MFR with $^{13}NH_3$ PET over standard relative MPI for predicting outcomes. Compared with Herzog et al. (14) study, the current study has a larger sample size (N = 677 vs. N = 229), similar percentage of male patients (61% vs. 69%), slightly fewer patients with known CAD (58% vs. 66%), a similar percentage of patients with MFR <2 (41% vs. 44.5%), but fewer patients had abnormal MPI (39% vs. 55%) and shorter follow-up. In line with Herzog et al. (14), our results show that: 1) in patients with normal and abnormal relative ^{82}Rb PET perfusion, subgroups with reduced MFR had a worse prognosis than their normal ^{82}Rb MFR counterparts; and 2) MFR on ^{82}Rb PET was an independent predictor of hard events (HR: 3.3, 95% CI: 1.1 to 9.5; p = 0.029) and MACE (HR: 2.4, 95% CI: 1.4 to 4.4; p = 0.003) after adjusting for relative MPI and other confounding variables. ^{82}Rb MFR improves risk stratification.

The present study also evaluated the effect of reducing MFR in different SSS subgroups. At any level of SSS, the percentage of MACE was highest among patients with the lowest MFR (<1.5) and statistically significant among those with an abnormal SSS (≥4). Among patients with cardiac death (n = 12), all had significantly reduced MFR (<1.5). Also, we assessed and observed that stress LVEF

Table 6 Multivariable Cox Models of MACE for Prognostic Value of MFR Compared With SSS

Parameter	Chi-Square test	p Value	Hazard Ratio	95% CI	Deviance Statistic
SSS* + baseline + stress LVEF†					830.718
SSS	8.6	0.003	2.4	1.3–4.4	
CCS angina class	9.5	0.002	2.1	1.3–3.4	
Stress LVEF	15.9	<0.001	0.85	0.79–0.92	
DM	4.1	0.043	1.6	1.02–2.60	
SSS* + baseline + stress LVEF† + MFR§					821.24‡
SSS	4.2	0.041	1.9	1.03–3.60	
CCS angina class	9.7	0.002	2.1	1.3–3.4	
Stress LVEF	9.3	0.002	0.88	0.81–0.96	
DM	3.2	0.074	1.5	0.96–2.50	
MFR	8.9	0.003	2.4	1.4–4.4	

*≥4 vs. <4. †Per 5-U increase. ‡p = 0.002 (likelihood ratio test). §<2 vs. ≥2.
Baseline = baseline demographic parameters; DM = diabetes mellitus; other abbreviations as in Tables 1 and 5.

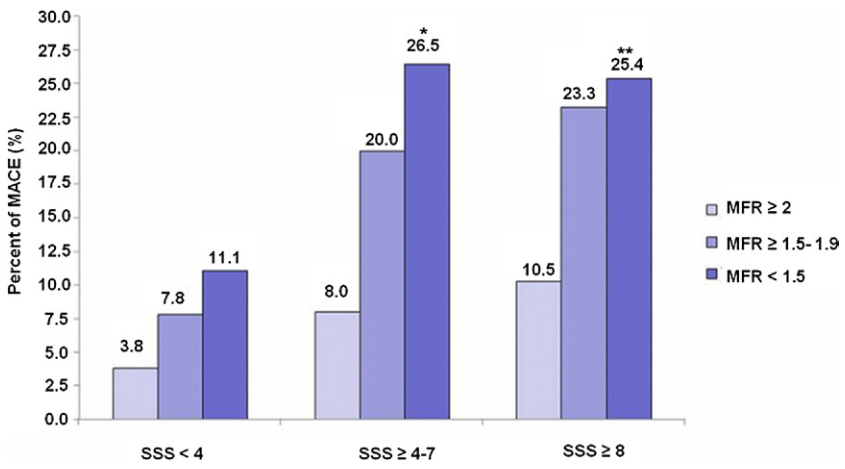

Figure 3 **MACE Within Subgroups of SSS for Different Levels of MFR**

At any level of SSS, the prevalence of MACE is higher in patients with the lowest MFR (<1.5) and statistically significant different compared with MFR ≥2 among patients with overt ischemia. *p = 0.028 for SSS ≥4 to 7 and MFR <1.5 versus MFR ≥2. **p = 0.002 for SSS ≥8 and MFR <1.5 versus MFR ≥2. MACE = major adverse cardiac events; other abbreviations as in Figure 1.

was a strong and independent predictor of adverse outcomes, extending findings of previous studies (5). Finally, we used ^{82}Rb, which, as a generator product, can be more widely distributed; thus, it has greater potential for wide clinical use compared with $^{13}NH_3$ and $H_2{}^{15}O$.

Clinical implications. Routine integration of ^{82}Rb MFR with relative MPI could represent a valuable tool for the clinician to better stratify a patient's risk of adverse cardiac events. Abnormal ^{82}Rb MFR means worse outcomes in any category of relative MPI, and this could affect management decisions for these patients. Even in those with mildly abnormal relative MPI who may be considered for medical therapy, impaired ^{82}Rb MFR had worse outcome (Fig. 3). Identification of impaired ^{82}Rb MFR in this group could have important impact on decisions for invasive angiography and revascularization. In patients with normal standard relative perfusion, reduced ^{82}Rb MFR would also indicate a worse prognosis, and this could also affect management and dictate the need for more aggressive medical therapy and closer follow-up of the patient. On the other hand, because patients with moderate to severe SSS on relative MPI may already be more likely to undergo invasive angiography and revascularization, the added value of impaired ^{82}Rb MFR may be less in this group but may still affect decisions for those who are at high risk of intervention. Because all cardiac deaths occurred in patients with severely reduced ^{82}Rb MFR (<1.5), it may also be that this signifies a particularly high-risk group. Further studies would be required to understand the impact of MFR on directing decision making to affect outcome.

Our rubidium generator and elution system (20) are different from those used in other laboratories, but the rubidium 1-tissue-compartment model used for flow quantification (24) should yield similar results with data from other systems. Our low-dose rubidium protocol was developed expressly to limit the peak dead-time losses with 3-dimensional PET while maintaining high-quality images (20). The rubidium activity can be infused over a longer interval to reduce the peak dead-time losses, improving the accuracy and precision of the resulting flow values. Three-dimensional mode PET imaging has been the approach used in our validation studies and assessment of intra- and interoperator variability (16). Three-dimensional imaging is now standard on all new PET scanners.

Study limitations. This study is observational and single centered; thus, there may be selection bias in patients referred for PET MPI. There were only 27 hard events, and overfitting the model for hard events may be a concern. The results need to be confirmed in a larger cohort with more hard events. PET MBF parameters were not available in the clinical report for the referring physicians during the course of this study period; management direction and decision making were not influenced by PET MBF quantification.

^{82}Rb has lower extraction fraction, which may affect the precision at hyperemic flow measurements, a higher positron range, which can reduce image resolution, and a relatively short half-life for imaging perfusion and function in patients with reduced left ventricular function. However, data support that flow quantification with ^{82}Rb is feasible, accurate, and reproducible (27–29) and has been validated against microspheres (30). As such, ^{82}Rb PET flow quantification has promise for risk stratification.

We focused primarily on global MFR that reflects diffuse (12,13) and potentially greater disease burden (7). Previous data in nonischemic and ischemic heart disease do suggest a potential prognostic value of global MFR measurements. We did explore regional MFR in patients with normal

global MFR and observed those with abnormal regional MFR had increased MACE, suggesting that there may be added value for regional MFR. Among those with impaired global MFR, it was uncommonly (6.2%) attributable to significant reduction in MFR in 1 vascular territory, thus making conclusive findings on regional MFR difficult. Larger studies will be required.

There is some interest in stress MBF as an independent parameter and indeed stress MBF is useful, but in the current study, MFR was the more significant predictor of outcome.

Conclusions

In a large cohort of patients referred for PET MPI to assess myocardial ischemia, assessment of MFR with ^{82}Rb yields independent and added prognostic information beyond relative MPI. Clinical integration of MFR with relative PET MPI will enhance risk stratification in this patient population.

Reprint requests and correspondence: Dr. Rob S. B. Beanlands, National Cardiac PET Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada. E-mail: rbeanlands@ottawaheart.ca.

REFERENCES

1. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress induced myocardial ischemia necessary? J Nucl Cardiol 2006;13:768–78.
2. Hachamovitch R, Kang X, Amanullah AM, et al. Prognostic implications of myocardial perfusion single photon emission computed tomography in the elderly. Circulation 2009;120:2163–5.
3. Marwick TH, Shan SJ, Patel AR, Go RT, Lauer MS. Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. Am J Cardiol 1997;80:865–70.
4. Yoshinaga K, Chow BJ, deKemp RA, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 2006;48:1029–39.
5. Lertsburapa K, Ahlberg AW, Heller GV, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. J Nucl Cardiol 2008;15:745–53.
6. Dorbala S, Hachamovitch R, Kwong RY, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. J Am Coll Cardiol Img 2009;2:846–54.
7. Berman D, Friedman JD, Germano G, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. J Nucl Cardiol 2007;14:521–8.
8. Parkash R, deKemp RA, Ruddy TD, et al. Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. J Nucl Cardiol 2004;11:440–9.
9. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.
10. Neglia D, Michelassi C, Trivieri MG, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation 2002;105:186–93.
11. Shikama N, Himi T, Yoshida K, et al. Prognostic utility of myocardial blood flow assessed by N-13 ammonia positron emission tomography in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 1999;84:434–9.
12. Olivotto I, Cecchi F, Camici PG, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006;47:1043–8.
13. Cecchi F, Olivotto I, Gistri R, et al. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003;349:1027–35.
14. Herzog BA, Husmann L, Kaufmann PA, et al. Long-term prognostic value of ^{13}N-ammonia myocardial perfusion PET: added value of coronary flow reserve. J Am Coll Cardiol 2009;54:150–6.
15. Tio R, van Veldhuisen DJ, Zijlstra F, et al. Comparison between the prognostic value of left ventricular function and myocardial perfusion reserve in patients with ischemic heart disease. J Nucl Med 2009;50:214–9.
16. Klein R, Renaud JM, Ziadi MC, et al. Intra- and inter-operator repeatability of myocardial blood flow and myocardial flow reserve measurements using rubidium-82 PET and a highly automated analysis program. J Nucl Cardiol 2010;17:600–17.
17. Dilsizian V, Bacharach SL, Beanlands RSB, et al. PET myocardial perfusion and metabolism clinical imaging. J Nucl Cardiol 2009;16:651.
18. Henzlova MJ, Cerqueira MD, Hansen CL, Taillefer R, Yao S. Imaging guidelines for nuclear cardiology procedures: stress protocols and tracers. J Nucl Cardiol 2009;16:331.
19. Schepis T, Gaemperli O, Adachi I, et al. Absolute quantification of myocardial blood flow with 13N-ammonia and 3-dimensional PET. J Nucl Med 2007;48:1783–9.
20. Klein R, deKemp RA, Beanlands RS, et al. Precision-controlled elution of a ^{82}Sr/^{82}Rb generator for cardiac perfusion imaging with positron emission tomography. Phys Med Biol 2007;52:659–73.
21. deKemp RA, Klein R, Renaud J, et al. 3D list mode cardiac PET for simultaneous quantification of myocardial blood flow and ventricular function. IEEE Nucl Sci Symp Conf Record, 2008;1:5215–8.
22. deKemp RA, Nahmias C. Automated determination of the left ventricular long axis in cardiac positron emission tomography. Physiol Meas 1996;17:95–108.
23. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.
24. Lortie M, Beanlands RS, deKemp RA, et al. Quantification of myocardial blood flow with 82-Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging 2007;34:1765–74.
25. Gewirtz H, Fischman AJ, Abraham S, et al. Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction. J Am Coll Cardiol 1994;23:851–9.
26. Gibbons RJ, Balady GJ, Bricker JT, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA guideline update for exercise testing. Circulation 2002;106:1883–92.
27. Beanlands RS, Nichol G, Huszti E, et al. F-18fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: a randomized, controlled trial (PARR-2). J Am Coll Cardiol 2007;50:2002–12.
28. Anagnostopoulos C, Dorbala S, Di Carli MF, et al. Quantitative relationship between coronary vasodilator reserve assessed by 82Rb PET imaging and coronary artery stenosis severity. Eur J Nucl Med Mol Imaging 2008;35:1593–601.
29. El Fakhri G, Dorbala S, Di Carli MF, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with ^{82}Rb PET: comparison with 13N-ammonia PET. J Nucl Med 2009;50:1062–71.
30. Lautamaki R, George RT, Kitagawa K, et al. Rubidium-82 PET-CT for quantitative assessment of myocardial blood flow: validation in a canine model of coronary artery stenosis. Eur J Nucl Med Mol Imaging 2009;36:576–86.

Key Words: myocardial flow reserve ▪ prognostic value ▪ rubidium-82 PET.